A Randomized, Controlled Study of a Simple, Once-Daily Regimen of Dihydroartemisinin-Piperaquine for the Treatment of Uncomplicated, Multidrug-Resistant Falciparum Malaria

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(See the editorial commentary by Kokwaro on pages 433–4)

Background. Dihydroartemisinin-piperaquine (DP) is a fixed-combination antimalarial drug increasingly deployed in Southeast Asia. The current regimen involves 4 doses given over 3 days. Simplification of the dose regimen should facilitate treatment adherence and thereby increase effectiveness.

Methods. In a randomized, controlled, 3-arm trial conducted along the northwestern border of Thailand, the standard 4-dose course of DP (DP4) was compared to an equivalent dose given as a once-daily regimen (DP3) and to the standard treatment of mefloquine-artesunate (MAS3).

Results. A total of 499 patients were included in the study. Times to fever and parasite clearance were similar in all groups. The PCR genotyping-adjusted cure rates at day 63 after treatment initiation were 95.7% (95% confidence interval [95% CI], 92.2%–98.9%) for MAS3, 100% for DP4, and 99.4% (95% CI, 98.1%–100%) for DP3. The DP4 and DP3 cure rates were significantly higher than that for MAS3 ($P = .008$ and $P = .03$, respectively). All regimens were well tolerated. There were 3 deaths (1 in the MAS3 group and 2 in the DP3 group), all of which were considered to be unrelated to treatment. Rates of other adverse events were comparable between the groups, except for diarrhea, which was more common in the DP4 group ($P = .05$ vs. the MAS3 group).

Conclusions. A once-daily, 3-dose regimen of DP is a highly efficacious treatment for multidrug-resistant falciparum malaria. This simple, safe, and relatively inexpensive fixed combination could become the treatment of choice for falciparum malaria.

Dihydroartemisinin-piperaquine (DP) is an artemisinin-containing, fixed-combination antimalarial drug developed in China. Recent randomized clinical trials in Cambodia, Vietnam, and Thailand indicate excellent tolerability and high cure rates against multidrug-resistant falciparum malaria [1–3]. DP is being used increasingly in Southeast Asia and is already part of national treatment recommendations in Cambodia and Vietnam.

Dihydroartemisinin is a highly active artemisinin derivative and the main in vivo metabolite of artesunate or artemether. Piperaquine is a bisquinoline that retains activity against chloroquine-resistant *Plasmodium falciparum*. Both drugs are highly active against asexual stages of all 4 species that cause malaria in humans.

Piperaquine replaced chloroquine as the first-line drug for malaria in China in 1978. The standard dose regimen in adults was a 600-mg loading dose followed by a 300-mg dose at 6 h and a 600-mg dose at 24 h. The main side effects of piperaquine were nausea, vomiting, and dizziness, which were generally mild and self-limiting [4]. It is estimated that 4 million Chinese patients were treated annually between 1978 and 1993; a total of 217 metric tons of piperaquine were used. Piperaquine was given as mass prophylaxis in some provinces, sometimes in combination with sulfadoxine-pyrimethamine. As a result of this intensive use, resistance

Received 9 February 2005; accepted 31 March 2005; electronically published 15 July 2005.

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Clinical Infectious Diseases 2005; 41:425–32

1058-4838/2005/4104-0001$15.00

of *P. falciparum* to piperaquine emerged in the mid-1980s. In the mid-1990s, piperaquine and dihydroartemisinin were added to trimethoprim and primaquine in various combinations, and evaluations of these regimens were performed in Vietnam (Tropical Medicine Institute of the Guangzhou University of Traditional Chinese Medicine, unpublished report). The manufacturer's current recommendations are to provide doses at 0 h, 6–8 h, 24 h, and 30–32 h. However, simple dose regimens facilitate treatment adherence, which is a critical determinant of effectiveness, and a once-daily treatment for 3 days would be preferable to the standard 4-dose regimen, if efficacy was not compromised. Artemisinin combination treatments (ACTs) need to expose 2 parasite asexual life-cycles to the artemisinin derivative to maximize the reduction in parasite numbers and thereby minimize the opportunity for resistance selection while providing optimum therapeutic responses [5]. ACTs require a 3-day regimen.

The aim of this study was to determine, in a large community-based evaluation, whether the DP combination could be given once-daily for 3 days without increasing the number and severity of adverse events or compromising efficacy.

PATIENTS AND METHODS

Patients aged 1–65 years with symptomatic *P. falciparum* monoinfection or *P. falciparum* mixed infections were recruited from 4 clinics along the Thai-Myanmar border, an area of unstable low and seasonal transmission of multidrug-resistant falciparum malaria [6]. Two clinics were in Mae La, a camp for 38,000 displaced persons mainly of the Karen ethnic group, and 2 clinics were in the Thai villages of Mawker Thai and Muruchai, where migrant workers from Myanmar come for treatment.

Exclusion criteria included pregnancy (on the basis of results of a urine pregnancy test for detection of β–human chorionic gonadotropin), lactation, $\geqslant$4% parasitized RBCs, signs or symptoms of severe malaria [7], and treatment with mefloquine in the previous 60 days. The verbal and written explanations of the study were in the patients' own languages (Karen or Burmese), and a consent form was signed or marked with a thumbprint (if the participant was unable to read or write). The study was approved by the Faculty of Tropical Medicine Ethical Committee at Mahidol University (Bangkok, Thailand) and the Oxford Tropical Research Ethics Committee (Oxford, United Kingdom).

The duration of symptoms before presentation, any drugs taken, and results of physical examination were recorded on a standard case record form. Patients underwent capillary blood sampling for malaria smear, hematocrit determination, and PCR genotyping. Thick and thin blood films were stained with Giemsa, and parasite counts were expressed as the number of parasites per 1000 RBCs or, for lower parasitemia, the number of parasites per 500 WBCs.

Antimalarial drug treatments. MAS3 consisted of artesunate (50-mg tablets [Guilin Factory no. 1]), 4mg/kg per day, and mefloquine (250-mg tablets of mefloquine hydrochloride [Mequin; Atlantic Laboratories]), 8 mg/kg per day for 3 days. DP4 consisted of a 4-dose regimen of dihydroartemisinin-piperaquine (Artekin [Holleykin Pharmaceuticals]). One tablet contains 40 mg of dihydroartemisinin and 320 mg of piperaquine. A weight-based regimen of 1.6 and 12.8 mg/kg per dose of dihydroartemisinin and piperaquine, respectively, rounded up or down to the nearest half tablet, was given at 0 h, 8 h, 24 h, and 48 h. DP3 consisted of a 3-dose regimen of dihydroartemisinin-piperaquine. Approximately the same total dose per kilogram as that in the DP4 regimen was given in 3 divided doses at 0 h, 24 h, and 48 h. Each dose was supervised, and it was repeated in full if vomiting occurred within 30 min after administration, or it was halved if the patient vomited 30 min to 1 h after administration.

Randomization. Patients were randomly allocated in blocks of 9 to the 3 groups. The randomization list was generated using Stata, version 7 (Stata), and the treatment allocation was concealed in sealed envelopes labeled with the study code. Laboratory staff reading the malaria smears had no knowledge of the treatment received.

Monitoring for adverse events. Adverse events were defined as signs and symptoms that occurred or became more severe after treatment started. Symptoms were screened at each visit. Serious adverse events were defined as death, a life-threatening reaction, an event requiring hospitalization or resulting in disability, or any medical event that might require intervention to prevent one of these outcomes. The causal relationship between the event and the study treatment was defined as unrelated, unlikely, possible, probable, or definite.

Follow-up. Tympanic temperature (Braun Thermoscan LF40) and blood smears were checked daily until fever and parasite clearance. Thereafter, patients attended the clinic weekly for clinical examination, symptom inquiry, malaria smear, and hematocrit determination. Non–*P. falciparum* infections occurring during the follow-up period were treated with chloroquine.

Management of reappearance of* P. falciparum *during follow-up. Patients in the MAS3 group with parasite reappearance were treated with a 7-day regimen of artesunate (2 mg/kg per day), which was combined with doxycycline (4 mg/kg once-daily) in patients >8 years old. Patients in either of the DP groups were treated with MAS3. PCR genotyping for allelic variation at 3 loci (merozoite surface proteins 1 and 2 and glutamate rich protein) was used to distinguish recrudescence from reinfection [8].

Study end points and statistical analysis. The main efficacy end points were the PCR-adjusted cure rates on follow-up day 63, as determined by a modified intention-to-treat analysis. End points were assessed using Kaplan-Meier survival analysis with a log-rank test for statistical significance. Patients arriving up to 1 week late for the final appointment were included in the day 63 analysis. Secondary efficacy end points were time to fever and time to parasite clearance.

Safety and tolerability end points were the incidences of anemia and other adverse events. Normally distributed continuous variables were compared using analysis of variance, and non-normally distributed continuous variables were compared by means of the Mann-Whitney *U* or the Kruskal-Wallis tests. Differences in proportions were compared using the 2-sided χ^2 test. Statistical programs used were SPSS for Windows, version 11.0 (SPSS), and Epi Info, version 1.0 (Centers for Disease Control and Prevention).

RESULTS

Between April 2003 and April 2004, 499 patients were included in the study, 199 in Mawker Thai, 88 in Muruchai, and 212 in Mae La camp. Of these patients, 166 were randomized to receive mefloquine plus artesunate (MAS3), 164 received the dihydroartemisinin-piperaquine standard-dose regimen (DP4), and 169 received the dihydroartemisinin-piperaquine 3-dose regimen (DP3). Data on enrollment, treatment allocation, and follow-up losses are shown in figure 1.

One patient from the DP4 group was removed from the study after 24 h of treatment, because the level of parasitemia increased from 2752 to 241,152 parasites/μL, which is defined as hyperparasitemia in this region [9]. The plasma piperaquine level at 24 h was 97 ng/mL, which is within the range associated with successful responses. The patient was treated with a 7-day course of artesunate-mefloquine (25 mg/kg per day) without further complications. One patient was found to have had *Plasmodium vivax* monoinfection when the slide was rechecked, and the patient was excluded from the analysis. Of the 497 patients, 96% completed 9 weeks of follow-up analysis. The main reason for loss to follow-up was change of address.

Baseline characteristics. The baseline characteristics of the study populations are summarized in table 1. There was no difference between characteristics of patients from the camp and those of patients from the migrant villages.

The mean ($\pm$SD) dihydroartemisinin and piperaquine doses received per treatment course were very similar in the 2 groups. Patients in the DP4 group received 6.9 $\pm$ 1.7 mg/kg dihydroartemisinin and 55.5 $\pm$ 13.3 mg/kg piperaquine, and patients in the DP3 group received 6.8 $\pm$ 1.3 mg/kg dihydroartemisinin and 54.1 $\pm$ 10.6 mg/kg piperaquine. The median number of visits to the clinic per patient was 12 in all groups (range, 1–14 visits).

Clinical and parasitological responses. Patients in all groups generally responded rapidly to treatment, with similar fever and parasite clearance times (table 2). PCR genotyping

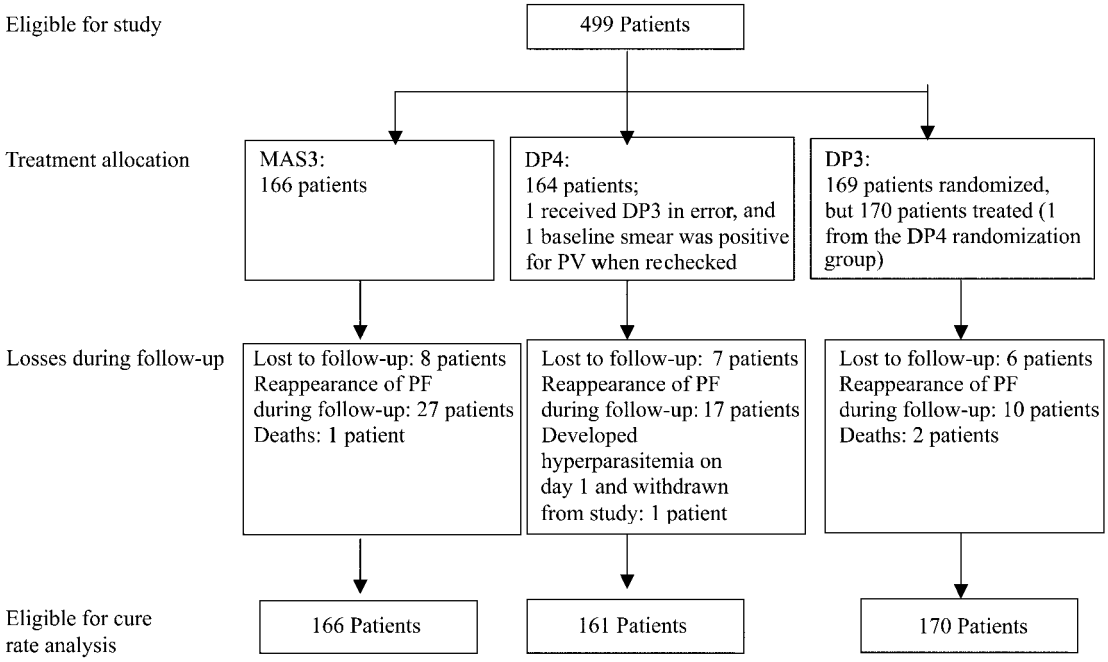

Figure 1. Patient flow in a randomized, controlled study comparing 3 treatment regimens, MAS3, DP4 and DP3, for the treatment of uncomplicated falciparum malaria. See Patients and Methods for a description of the antimalarial treatments. PF, *Plasmodium falciparum;* PV, *Plasmodium vivax.*

Table 1. Patient characteristics at baseline, by antimalarial treatment received.

Characteristic	MAS3	DP4	DP3
All patients			
No. enrolled	166	163	170
Male sex, no. (%)	102 (61.4)	96 (58.9)	104 (61.2)
Age, years, median (range)	19 (1–55)	22 (2–65)	21 (3–57)
Weight, kg, median (range)	43 (7–66)	45 (10–78)	45 (10–65)
Fever duration before admission, days, median (range)[a]	2 (1–7)	2 (0.5–14)	2 (1–14)
Geometric mean parasitemia level, parasites/μL (range)	10,678 (100–229,087)	11,899 (100–223,872)	9005 (83–199,526)
Mixed infection at admission, no. (%)	16 (9.6)	15 (9.2)	16 (9.4)
Hematocrit, %, mean ± SD	37 ± 6.0	38 ± 6.0	37 ± 6.1
Children aged <15 years			
No. enrolled	63	51	47
Male sex, no. (%)	39 (61.9)	27 (52.9)	30 (63.8)
Age, years, median (range)	8 (1–14)	10 (2–14)	10 (3–14)
Weight, kg, median (range)	20 (7–51)	24 (10–48)	25 (10–50)
Geometric mean parasitemia level, parasites/μL (range)	11,569 (100–158,489)	19,738 (263–218,776)	15,714 (363–131,826)
Hematocrit, %, mean ± SD	34 ± 5.6	35 ± 5.5	34 ± 6.6

NOTE. See Patients and Methods for a description of the antimalarial treatments.

[a] *Plasmodium falciparum* infection plus *Plasmodium vivax* and/or *Plasmodium malariae* infection.

showed 42 novel infections, 8 recrudescent infections, and 2 indeterminate genotyping results. Four patients with indeterminate results or missing samples were censored from the cure rate analysis on the day of parasite reappearance.

The PCR-adjusted cure rates at follow-up day 63 were 95.7% for MAS3 (95% CI, 92.2%–98.9%), 100% for DP4 ($P = .008$ vs. MAS3), and 99.4% for DP3 (95% CI, 98.1%–100%; $P = .03$ vs. MAS3).

All treatment failures in the MAS3 group occurred between days 14 and 28 of follow-up, whereas those in the DP groups occurred after day 35 (table 3). The baseline characteristics of patients who did and those who did not successfully respond to treatment did not differ.

Anemia. The absolute changes in hematocrit between admission and each follow-up day were calculated for each individual patient and were summarized as median values for

Table 2. Times to fever and parasite clearance in patients, by antimalarial treatment received.

Fever and parasite clearance, by treatment day	MAS3 (n = 166)	DP4 (n = 163)	DP3 (n = 170)	P[a]
No. (%) of patients with fever[b]				
Day 0	52 (31)	63 (39)	64 (38)	.95
Day 1	12 (7)	11 (7)	16 (10)	.96
Day 2	2 (1)	4 (3)	3 (2)	
No. (%) of patients with positive smear results				
Day 0	166	162[c]	170	
Day 1	140 (84)	120 (74)	135 (79)	.88
Day 2	28 (17)	33 (20)	32 (19)	.99
Day 3	4 (2)	4 (2)	4 (2)	

NOTE. See Patients and Methods for a description of the antimalarial treatments. Treatment was initiated on day 0.

[a] By the χ^2 test.

[b] Tympanic temperature, >37.5°C.

[c] One patient was excluded because *Plasmodium vivax* was detected when the slide was rechecked.

Table 3. Number of PCR-confirmed cases of treatment failure and reinfection.

Characteristic, by treatment	No. of cases, by day after treatment initiation								
	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 56	Day 63	Total
Treatment failure									
MAS3	2	3[a]	2	…	…	…	…	…	7
DP4[b]	…	…	…	…	…	…	…	…	0
DP3	…	…	…	…	…	…	1	…	1
Reinfection									
MAS3	1	3	1	2	4	4	2	2	19
DP4	…	…	1	2	5	1	2	3	14
DP3	…	1	1	1	2	1	2	1	9

NOTE. See Patients and Methods for a description of the antimalarial treatments. Treatment was initiated on day 0.

[a] The day-21 sample was missing for one of the patients.

[b] One PCR result on day 35 was indeterminate, and day-63 samples were missing for 2 of the patients.

each treatment group. There was a decrease in hematocrit between days 0 and 7, followed by a recovery in all groups (figure 2). Two patients required a blood transfusion.

Gametocyte carriage. Thirty-six patients had patent gametocytemia at the time of presentation; 13 (8%) were in the MAS3 group, 13 (8%) were in the DP4 group, and 10 (6%) were in the DP3 group. Of the 93% of patients without gametocytemia at baseline, 1 (1%) in the MAS3 group, 2 (1%) in the DP4 group, and 7 (4%) in the DP3 group developed patent gametocytemia during the week after treatment ($P = .054$). Between follow-up days 14 and 63, no gametocytes were detected in any of these patients. The person-gametocyte weeks (per 1000 person-weeks) in the MAS3, DP4, and DP3 groups were 0, 10, and 10 respectively.

Mixed infections. Forty-seven patients had a mixed infection with *P. vivax* (45 patients) or *Plasmodium malariae* (2 patients) at enrollment. Of these patients, 23 (52%) had a second *P. vivax* infection or relapse during follow-up. Eight were in the MAS3 group, with a median time to appearance of 42 days (range, 28–63 days); 7 were in the DP4 group, with a median time to appearance of 56 days (range, 35–63 days); and 8 were in the DP3 group, with a median time to appearance of 49 days (range, 35–63 days).

During follow-up, 104 (23%) of 452 patients with *P. falciparum* monoinfection at admission developed *P. vivax* infection, and 2 patients developed *P. malariae* infection. Thirty patients were in the MAS3 group, with a median time to appearance of 49 days (range, 28–63 days); 36 were in the DP4 group, with a median time to appearance of 56 days (range, 21–63 days); and 38 were in the DP3 group, with a median time to appearance of 49 days (range, 35–63 days) ($P = .65$ for the MAS3 group vs. the DP groups).

Adverse events. There were 15 serious adverse events (table 4). Three patients died during the study, 2 in the DP3 group and 1 in the MAS3 group.

A 43-year-old woman in the DP3 group who had a history of hypertension died in the clinic <24 h after admission. The parasitemia level at admission was 12,560 parasites/μL, with 3 schizonts/500 WBCs and malaria pigment. Her condition deteriorated overnight, and she complained of generalized weakness and numbness. Physical examination revealed that she was cold and pale, with an irregular heart rate of 108 beats/min and an unrecordable blood pressure. Her Glasgow Coma Score was 15. There were no respiratory symptoms. She had a cardiac arrest 4 h later and could not be resuscitated. The postmortem parasitemia level was 262,248 parasites/μL. Analysis of stored plasma specimens obtained at admission revealed that she was

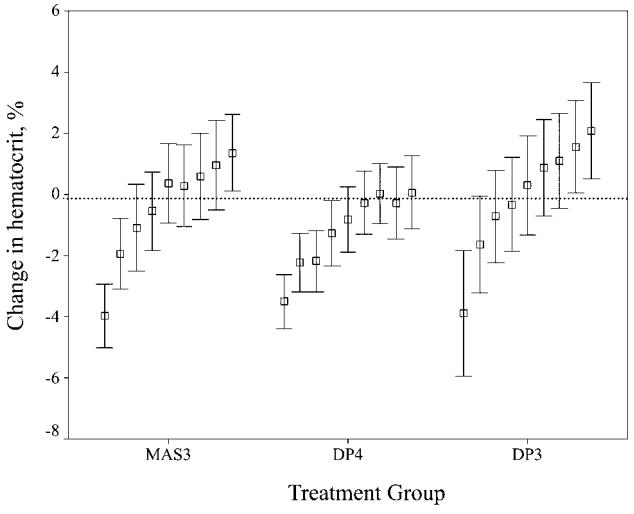

Figure 2. The absolute changes in hematocrit between admission and each follow-up day were calculated for each individual patient and were summarized as median values for each treatment group (see Patients and Methods for a description of the antimalarial treatments). Data points for each treatment represent a series of 9 observations between weeks 1 and 9 of follow-up. *Boxes,* median values; *whiskers,* 95% CIs.

Table 4. Serious adverse events associated with 3 antimalarial treatments.

Patient	Age in years, sex	Antimalarial treatment	Day of onset	Day of resolution	Hospitalized	Adverse events	
						Type(s)	Relationship to study treatment
1	13, M	MAS3	6	…	Yes	Death[a]	Unrelated
2	3, M	MAS3	2	2	Yes	Hematocrit, 17%; required blood transfusion	Unrelated
3	5, M	MAS3	1	3	Yes	Probable febrile convulsion	Unrelated
4	50, F	MAS3	49	…	No	Presented with spontaneous bruising, jaundice, and hepatosplenomegaly; platelet count, 92,000 platelets/mL; slightly abnormal liver function; treated with vitamin K; presumptive diagnosis of coagulopathy secondary to alcoholic liver disease.	Unrelated
5	30, M	DP4	4	13	Yes	Fever, rash, and meningism; responded to intravenous chloramphenicol; presumptive diagnosis of bacterial sepsis (CSF microscopy findings were normal)	Unrelated
6	2, M	DP4	1	1	No	Short seizure at home, with fever; probable febrile convulsion	Unlikely
7	12, F	DP4	38	42	Yes	Suspected leptospirosis; responded to doxycycline	Unrelated
8	26, M	DP4	22	22	No	Small hematemesis	Unrelated
9	43, F	DP3	1	…	Yes	Death[a]	Unrelated
10	13, F	DP3	7	…	No	Death[a]	Unrelated
11	5, M	DP3	42	63	No	Nephritic syndrome; probable acute post-streptococcal glomerulonephritis	Unrelated
12	34, M	DP3	28	29	Yes	Hematocrit, 15%; required blood transfusion.	Unrelated
13	11, M	DP3	0	2	Yes	Vomiting that required intravenous rehydration	Probable
14	26, M	DP3	29	36	Yes	Respiratory infection	Unrelated
15	18, F	DP3	7	10	Yes	Severe epigastric pain; normal upper abdominal ultrasound findings; the pain settled with antacids	Unlikely

NOTE. See Patients and Methods for a description of the antimalarial treatments.

[a] See Results for additional details.

acidotic (total CO_2 concentration, 16 mEq/L). Tests of blood collected 3 h after death showed renal impairment (plasma urea nitrogen concentration, 40 mg/dL [normal range, 8–23 mg/dL]; creatinine concentration, 4.3 mg/dL [normal range, 0.5–1.5 mg/dL]) and some evidence of hepatic impairment (aspartate aminotransferase concentration, 251 U/L [normal range, 5–40 U/L]); alanine aminotransferase concentration, 152 U/L [normal range, 5–40 U/L]). The hemoglobin level was 8.2 g/dL, with a WBC count of 17,100 cells/mL (78.9% neutrophils) and a platelet count of 22,000 platelets/μL. Microscopic analysis of a CSF specimen revealed a WBC count of 100 cells/mm^3 (80% lymphocytes) and an RBC count of 290 cells/mm^3. Blood culture showed no growth. Plasma piperaquine levels 7 and 12 h after dosing were 72 and 22 ng/mL, respectively, which are within the expected range. There was no piperaquine detectable in the CSF.

The 2 other deaths occurred away from the clinics, and verbal autopsies were performed using the World Health Organization standard verbal autopsy method for investigating causes of death in children [10]. A 13-year-old girl, also in the DP3 group, had an uncomplicated course immediately after treatment, with defervescence, parasite clearance, and clinical improvement by the third day. Two days later, she developed fever again, followed 48 h later by headache, abdominal pain, vomiting, and diarrhea. She died that evening before seeking any treatment. A smear of a blood sample obtained several hours postmortem was negative for malaria parasites.

The third death involved a 13-year-old boy in the MAS3 group. He was afebrile, malaria-smear negative, and clinically well by the third day of treatment. He traveled from Thailand to Myanmar to visit relatives. Two days later, he complained of a sudden onset of abdominal pain without fever. He was reported to have deteriorated rapidly with worsening abdominal pain and distension, jaundice, and anuria, and he died within a few hours. None of the 3 patients were known to be taking other medications apart from simple antipyretics.

There was 1 inadvertent pregnancy exposure in a 26-year-old multiparous woman. The date of conception estimated

Table 5. Selected nonsevere adverse events reported up to day 28 after treatment initiation, by antimalarial drug received.

Adverse event	MAS3	DP4	DP3	P[a]
Diarrhea	8 (4.8)[b]	20 (12.3)[b]	13 (7.6)	.046
Urticaria	0	1 (0.6)	2 (1.2)	.378
Nausea	22 (13.3)	21 (12.9)	16 (9.4)	.484
Vomiting	18 (10.8)	13 (8.0)	10 (5.9)	.252
Abdominal pain	13 (7.8)	13 (8.0)	15 (8.8)	.938
Sleep disturbance	26 (15.7)	25 (15.3)	17 (10.0)	.236
Dizziness	28 (16.9)	18 (11.0)	19 (11.2)	.198

NOTE. Data are no. (%) of patients. See Patients and Methods for a description of the antimalarial treatments.

[a] By the χ^2 test.

[b] $P = .026$ for the MAS3 group vs. the DP4 group.

from an 18-week ultrasonogram was the day after the final dose of DP. A 2.3-kg male infant was delivered at home at 41 weeks gestation. Findings of routine examination were normal, apart from low birth weight.

Other adverse events. Early vomiting (i.e., up to 1 h after dose administration) occured in <3% of patients in all groups and did not necessitate change of treatment. Diarrhea within the first 28 days of follow-up was reported by 12% of patients in the DP4 group, 5% in the MAS3 group, and 8% in the DP3 group. The difference between the MAS3 and DP4 groups was statistically significant ($P = .026$). Diarrhea occurred mainly on days 1–3 after treatment and was mild; there was no relationship to age or weight. The frequencies of other adverse events were similar between groups. The most commonly reported symptoms were dizziness, sleep disturbance, and nausea (table 5). Three patients treated with DP developed an urticarial rash.

DISCUSSION

In this study, a once-daily, 3-dose treatment of DP was a simple, highly efficacious, and generally well-tolerated treatment for uncomplicated, multidrug-resistant falciparum malaria in adults and children.

Three deaths occurred during this study. Two occurred in the DP3 group. It was not possible to ascertain the cause of either death, although the sudden death of the previously hypertensive 41-year-old woman probably resulted from severe malaria. Whether she had significant preexisting renal impairment or other end-organ damage from hypertension that may have increased the risk of fatal outcome is not known. It is unlikely that this fatality was related to DP treatment; there was no evidence of type I hypersensitivity, and significant cardiotoxicity has not been described with piperaquine [3, 11]. The deaths of the other 2 patients were considered as being unlikely to have resulted from malaria or its treatment. There was also a death following DP treatment in a study in Cambodia [1]. An 8-year-old boy became malaria-smear negative within 2 days after starting treatment but remained febrile. He became hypotensive and died 2 days later. The authors surmised that concomitant bacterial sepsis was the probable cause [1].

The other serious adverse events were unlikely to be related to the study drugs (table 4). The seizure in the 2-year-old child treated with DP is most likely to have been a febrile convulsion. More serious adverse events have been reported here than elsewhere with this drug; however, this may be the result of reporting bias and the duration of the follow-up period. Adverse event reporting from clinical trials is nonstandardized, with a tendency to underreport events thought to be unrelated to the study drug [12].

Are there enough data to believe that DP is safe? The history of extensive piperaquine use in China, the excellent safety profile of the artemisinin derivatives, and the fact that this drug combination is in routine use in Vietnam with no reports of serious adverse events (although with the acknowledgment that there are limited resources available for pharmacovigilance) suggest that it is, although more supporting safety data from clinical trials would be reassuring.

It was not possible to identify any predictors of treatment failure in the DP groups, because the treatment was highly effective. Indeed, both DP regimens were significantly more effective than the standard regimen of mefloquine-artesunate in this trial. Whether there truly is a higher cure rate will require additional, larger studies—but if its efficacy is confirmed, DP would be the most effective antimalarial treatment currently available.

The effects of DP in suppressing relapses of *P. vivax* infection in patients with mixed infections at baseline were similar to those observed with chloroquine, with reappearance of *P. vivax* ~7 weeks after starting therapy [13]. This suggests suppression of the first relapse 3 weeks after treatment initiation, as reported elsewhere after treatment with slowly eliminated drugs [14]. The low prevalence of gametocyte carriage reflects the well-known gametocytocidal properties of the artemisinin derivatives [15] and is an important component of their activity.

DP was well tolerated, with a low incidence of mild side effects. The excess number of diarrhea episodes found in the DP4 group (in which a higher dose of piperaquine was given on day 0) is plausible, given the known toxicity profile of piperaquine. There was no evidence of increased toxicity in children, which is reassuring, although no children who weighed <7 kg were randomized into any of the DP groups, and more information on safety and efficacy in young children is clearly needed. Use of the current formulation means that dosing in young children involves crushing tablets. However, a pediatric formulation is under development. Very high cure rates with DP have now been described in several studies that were conducted in areas in which multidrug-resistant malaria is present.

This study confirms the remarkably good efficacy of DP that can be obtained with a very simple 3-day, once-daily regimen. Although further studies will be needed to establish the safety profile of DP with confidence, the evidence to date suggests excellent tolerability. The projected cost of DP relative to other artemisinin-based combinations is low. Taken together, these observations provide a compelling argument that DP is one of the leading combination antimalarial drugs.

Acknowledgments

We thank all of the patients who took part in the study, as well as the staff of the Shoklo Malaria Research Unit, especially Saw Yoe Moo for data entry, Khun Ratsuda Yaporn and Khun Kamajittra Jenjaroen for their work in PCR analysis, and Niklas Lindegårdh for drug assays. Artekin was kindly provided by Holleykin Pharmaceutical, Guangzhou, China.

Financial support. The study was partially supported by Medicines for Malaria Venture. The Shoklo Malaria Research Unit is part of the Wellcome Trust-Mahidol University, Oxford Tropical Medicine Research Programme, funded by the Wellcome Trust of Great Britain.

Potential conflicts of interest. All authors: no conflicts.

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